

# Adenomyoepithelioma With Myoepithelial Carcinoma of the Breast With Axillary Lymph Node Metastasis: Two Case Reports and Review of the Literature

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**Objectives:** Adenomyoepithelioma (AME) of the breast exhibits characteristic proliferation of the epithelial and myoepithelial cells. Most AMEs are benign, but the 2 inherent cell types can become malignant. The present study reports 2 cases of AME with myoepithelial carcinoma of the breast, one with axillary lymph node metastasis.

**Methods:** A modified radical mastectomy was performed in a 67-year-old woman, because a sentinel lymph node biopsy revealed one metastatic lymph node composed of a myoepithelial carcinoma component. Despite receiving radiotherapy and chemotherapy, the patient died from lung and brain metastases 21 months later. In the second case, breast-conserving surgery with sentinel lymph node biopsy was performed in a 55-year-old woman. Following additional treatment with radiotherapy and chemotherapy, there were no signs of recurrence or metastasis. **Results:** The tumors of the 2 patients were diagnosed as malignant, based on their high mitotic rate and severe nuclear atypia.

**Conclusions:** Based on previously reported cases with distant metastases, the prognosis of myoepithelial carcinoma is poor. Myoepithelial carcinoma should be followed up with careful screening and treated aggressively.

*Key words:* Adenomyoepithelioma – Myoepithelial carcinoma – Breast

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**A**denomyoepithelioma (AME) of the breast is a rare tumor that is characterized by biphasic proliferation of the epithelial and myoepithelial cells.<sup>1</sup> In rare instances, the epithelial, the myoepithelial, or both components of an AME may become malignant.<sup>1,2</sup> Myoepithelial carcinoma (malignant myoepithelioma) is a malignant lesion composed of spindled myoepithelial cells with infiltrating margins and high mitotic activity.<sup>1</sup> According to the fourth edition of the World Health Organization (WHO) classification, myoepithelial carcinoma is classified under metaplastic carcinoma.<sup>2</sup> It is diagnosed through recognition of the overlapping morphologic and immunophenotypical characteristics.<sup>1</sup>

Most AMEs and myoepithelial carcinoma tends to present as a painless, palpable mass. A rapid growing mass is highly suggestive of myoepithelial carcinoma. Although myoepithelial carcinoma of breast still does not have an established standard treatment, the basic treatment for primary tumor is surgery. In previous reports, a few cases were treated with chemotherapy, but the response has not been favorable.<sup>1,3</sup> Certain studies have reported myoepithelial carcinoma with local recurrence and metastasis after the initial surgery.<sup>1,3</sup> Local recurrence may occasionally occur, but distant metastasis is extremely rare and is usually hematogenous.<sup>3</sup>

We report herein 2 cases of AME with myoepithelial carcinoma of the breast, of which one had axillary lymph node and distant metastasis.

## Case report

### Case 1

#### Clinical summary

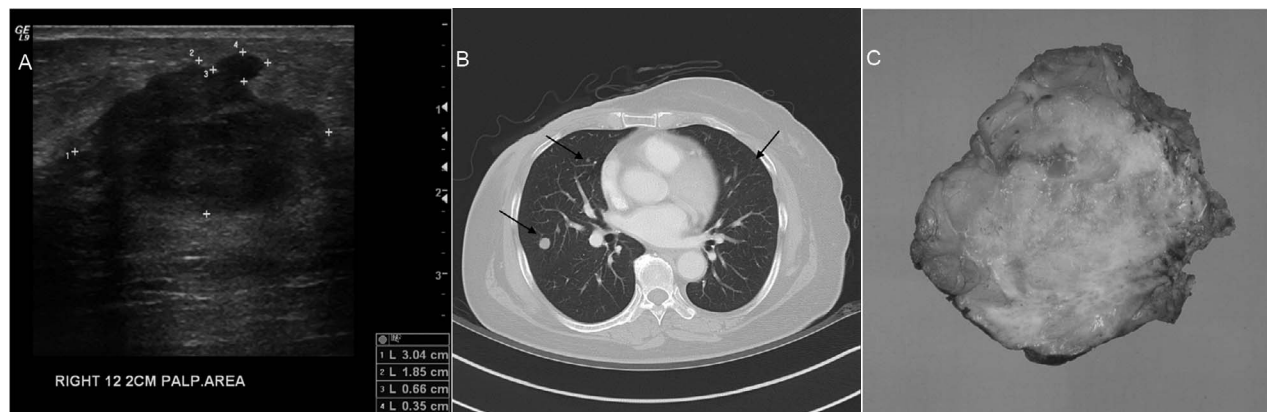
A 67-year-old woman presented to \*\*\*\*\* Hospital (\*\*\*\*\*, \*\*\*, \*\*\*\*\*) with a large palpable mass in the upper midregion of the right breast. Physical examination indicated an ~4- × 3-cm firm, tender mass. Mammography showed a 4-cm irregularly shaped hyperdense mass with indistinct margins in the upper midportion of the right breast. On ultrasound examination, a 3.6-cm inhomogeneous, irregularly marginated, and hypoechoic mass was located at the 12 o'clock position of the right breast (Fig. 1A). The patient underwent an ultrasound-guided core-needle biopsy, and the pathologic diagnosis was of a benign pleomorphic adenoma-like, salivary gland-type neoplasm. Elective surgery was planned, but the patient did not return to the hospital for 6 months due to poor economic status. On returning, the patient underwent a lumpectomy, and the surgical specimen showed a gray-white 5- ×

4-cm mass on the cut surface. The breast tumor was histologically diagnosed as myoepithelial carcinoma with an AME component, and the inferior and lateral resection margins of the tumor were positive. The patient then underwent a modified radical mastectomy. On sentinel lymph node biopsy, one of the sentinel lymph nodes showed metastasis, and an axillary lymph node dissection was performed. On pathologic examination, 2 residual tumors diagnosed as AME with myoepithelial carcinoma were observed, and 1 of the 14 dissected axillary lymph nodes was metastatic. Following surgery, the patient underwent adjuvant chemotherapy with 4 cycles of a docetaxel and cyclophosphamide regimen (docetaxel 75 mg/m<sup>2</sup> intravenous [IV] infusion plus cyclophosphamide 600 mg/m<sup>2</sup> IV infusion given on day 1 for 3 weeks), without doxorubicine, due to a myocardial infarction. After 6 months, multiple lung metastases were observed on follow-up chest computed tomography (CT) scans (Fig. 1B). The patient therefore underwent palliative chemotherapy with 4 cycles of a gemcitabine and cisplatin regimen (gemcitabine 700 mg/m<sup>2</sup> IV infusion plus cisplatin 30 mg/m<sup>2</sup> infusion given on days 1 and 8 every 3 weeks). At 18 months after surgery, brain metastasis was observed, and brain radiotherapy (whole-brain radiotherapy of 30 Gy in 10 fractions over 2 weeks) and palliative chemotherapy with vinorelbine (vinorelbine 30 mg/m<sup>2</sup> IV on days 1 and 8 every 3 weeks) were performed. However, the patient died 3 months after the diagnosis of brain metastasis and 21 months after the first surgery.

#### Pathologic diagnosis

Macroscopically, serial sections revealed a poorly demarcated, multilobulating, whitish-gray, myxoid mass, measuring 5 × 4.2 cm. The cut surface of the mass showed multifocal, small cystic spaces, filled with necrotic fluid (Fig. 1C).

Microscopically, the tumor showed multilobulated collections of monomorphic, polygonal, epithelial, or spindled cells, with multiple pseudocystic necrotic foci (Fig. 2A). The tumor cells demonstrated high mitotic activity and marked pleomorphism (Fig. 2B). The number of mitoses was 16 per 10 high-power fields (HPFs). A few of them encircled and entrapped the normal glands. The tumor showed bicellular proliferation of the epithelial and myoepithelial cells (Fig. 2C). In 1 lymph node, metastatic myoepithelial carcinoma of the breast was observed on hematoxylin and eosin staining (Fig. 2D). The immunohistochemical staining (Fig. 3) of the AME component was positive for Cam5.2, epithelial



**Fig. 1** Imaging studies and gross photograph of case 1. (A) Ultrasonographic examination of case 1 reveals an indistinctly marginated, irregularly shaped, heterogeneous, hypoechoic mass with posterior enhancement. (B) On CT scan 3 months later, bilateral multiple metastatic lung tumors were found. Arrows indicate metastatic lung nodules. (C) Gross appearance of the tumor reveals a poorly demarcated, multilobulating, whitish gray mass.

membrane antigen (EMA), and cytokeratin 5/6 (CK5/6) in the epithelial cells and for CK5/6, CD10, and p63 in the myoepithelial cells. The myoepithelial carcinoma component was positive for CK5/6, CD10, and p63. The tumor cells were negative for estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 (HER2)/neu on immunohistochemical staining.

## Case 2

### Clinical summary

A 55-year-old woman presented to \*\*\*\*\* Hospital with a large palpable mass in the upper inner quadrant of the right breast. Physical examination indicated an ~1.5-cm firm mass. On mammography, ultrasound examination, and breast magnetic resonance imaging, a 2.3-cm, spiculated, irregularly shaped, peripheral enhancing mass was observed in the right upper midportion of the breast (Fig. 4A and 4B). The patient underwent an ultrasound-guided core-needle biopsy, and the pathologic diagnosis was of an epithelial-myoepithelial tumor with myoepithelial overgrowth. The patient then underwent breast-conserving surgery with sentinel lymph node biopsy. The breast tumor was histologically diagnosed as AME with myoepithelial carcinoma, with clean resection margins and no sentinel lymph node metastasis. The patient underwent adjuvant radiotherapy (external beam radiotherapy with 45 Gy for 6 weeks) and 4 cycles of anthracycline-based chemotherapy (doxorubicin 60 mg/m<sup>2</sup> IV infusion plus cyclophosphamide 600 mg/m<sup>2</sup> infusion given on day 1 every 3 weeks).

After 1 year, this patient currently shows no evidence of recurrence or metastasis.

### Pathologic diagnosis

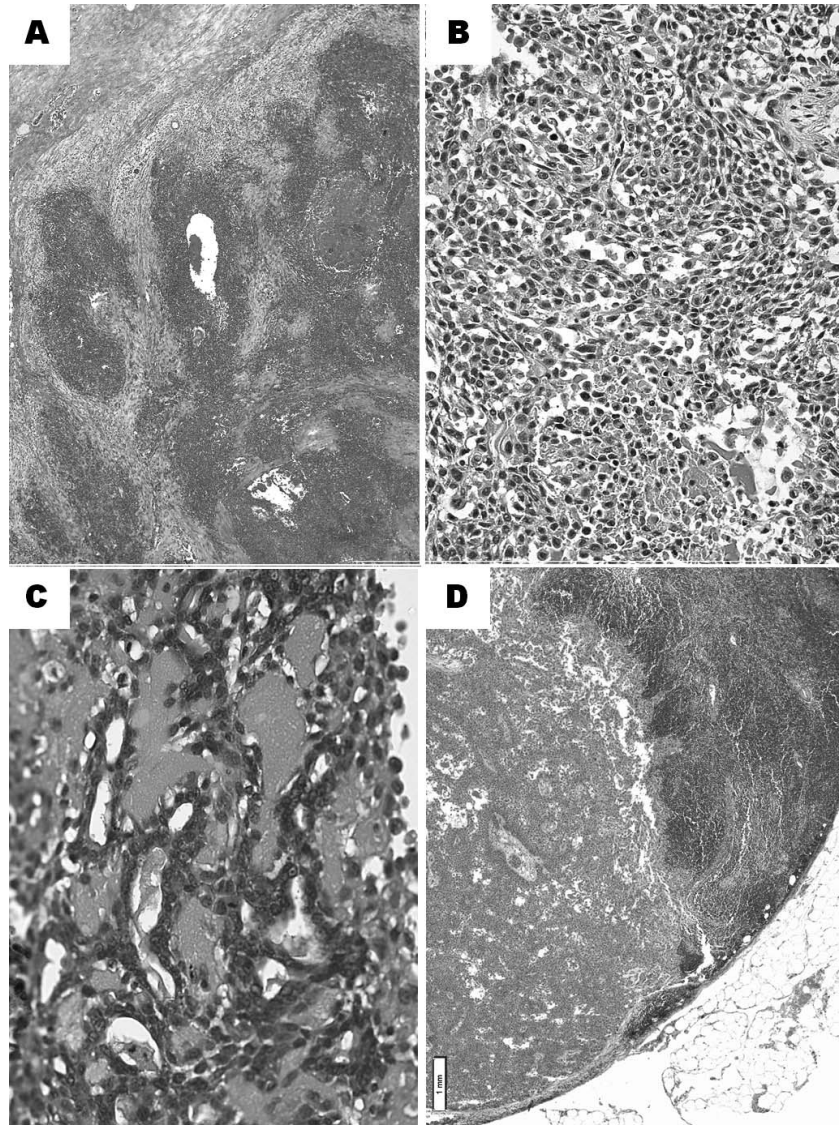
Macroscopically, the tumor was a relatively circumscribed, ovoid, grayish mass, measuring 1.8 × 1.4 cm with multifocal hemorrhagic change (Fig 4C).

Microscopically, the tumor was composed of a ductal component and a spindle cell component. The ductal component was small, tubular, or cystically dilated, with epithelial and myoepithelial cell components. The spindle cells were epithelioid and vaguely clustered and fibroblastic or smooth muscle-like. The myoepithelial carcinoma was composed mostly of a dominant spindle cell component with admixed ductal cells (Fig. 5A). The stromal cells showed frequent mitoses (10/10 HPF), necrosis, and 30%–40% Ki-67 labeling. On immunohistochemical staining, the spindle cell components were positive for smooth muscle marker (smooth muscle actin [SMA]), epithelial markers (CK and high-molecular weight CK), and myoepithelial cell marker (p63) (Fig. 5B and 5C). Certain cells were positive for S-100 protein, but there were no glial fibrillary acidic protein-positive cells.

### Discussion

AMEs are rare tumors, and myoepithelial carcinoma arising in an AME has been reported only in individual case reports and studies of fewer than 5 cases.<sup>1,3–7</sup> AME is composed of a proliferation of

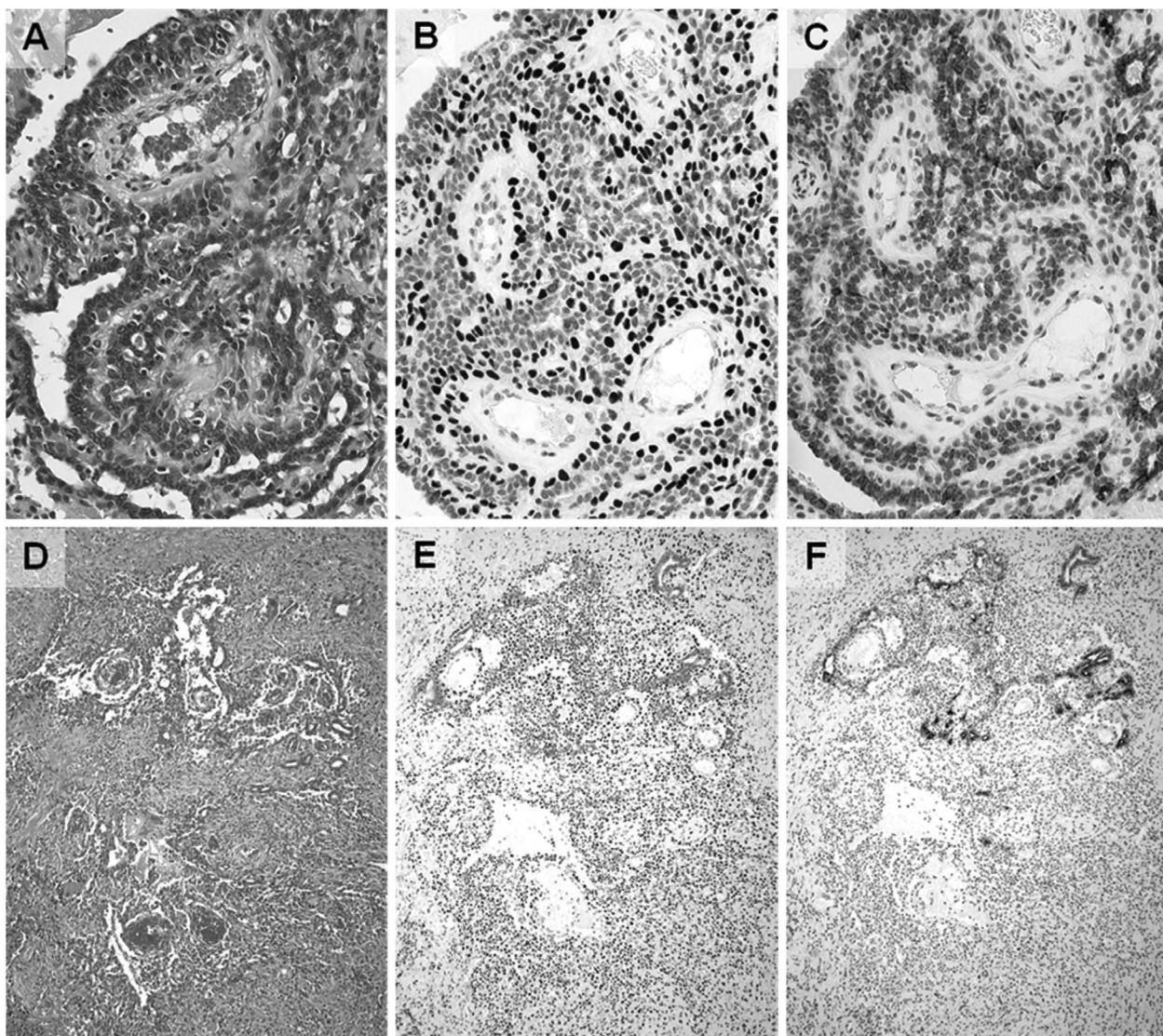
**Fig. 2** (A) Low-power photomicrograph shows myoepithelial carcinoma (hematoxylin and eosin [H&E];  $\times 40$  magnification). (B) High-power photomicrograph shows myoepithelial carcinoma component with solid proliferation of polygonal or spindle tumor cells with mitotic changes (H&E;  $\times 200$  magnification). (C) High-power photomicrograph shows adenomyoepithelial component. Benign adenomyoepithelioma showing the tubular ducts surrounded by myoepithelial cells that have clear cytoplasm (H&E,  $\times 200$  magnification). (D) Low-power photomicrograph shows lymph node metastases with myoepithelial carcinoma. In the axillary lymph node, monophasic spindle cells proliferate, showing similar histologic features as in myoepithelial carcinoma of the breast (H&E,  $\times 40$  magnification).



layers of myoepithelial cells around epithelium-lined spaces.<sup>2</sup> Either one or both cell types can undergo malignant transformation.<sup>1</sup> According to the fourth edition of the WHO classification, the malignant transformation of AME can be divided into 3 subtypes: (1) epithelial type; (2) myoepithelial type; and (3) epithelial and myoepithelial type.<sup>2</sup> In the present study cases, the myoepithelial components underwent malignant transformation; thus, these are instances of AME with myoepithelial carcinoma.

Using double immunofluorescence labeling, the study by Hungermann *et al* showed that adenomyoepithelial tumor cells coexpress basal type CK5/6 either alone or in combination with glandular CK8/18 or SMA.<sup>7</sup> The study suggested that

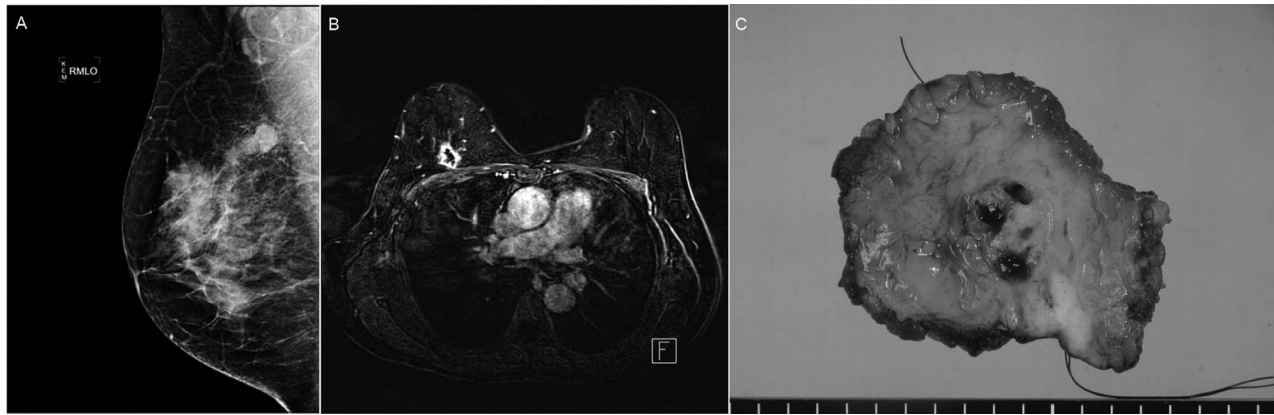
CK5/6-positive cells may be an essential component in the histogenesis of AME and that biphasic epithelial and myoepithelial tumors may be a consequence of transformation events in CK5-positive stem cells or adult pluripotent progenitor cells, which have undergone divergent differentiation into fully secretory luminal and myoepithelial cells. In the present cases, the immunohistochemical staining of the AME component was positive for CAM5.2, EMA, and CK5/6 in the epithelial cells and for CK5/6, CD10, and p63 in the myoepithelial cells. The tumor cells demonstrated high mitotic activity and marked pleomorphism, and thus the tumor was diagnosed as a myoepithelial carcinoma.



**Fig. 3** H&E and immunohistochemical stains of case 1. (A) High-power photomicrograph showing an adenomyoepithelial component on H&E staining. Adenomyoepithelioma showing a relatively uniform admixture of small ducts and surrounding myoepithelial cells ( $\times 200$  magnification). (B) High-power photomicrograph showing an adenomyoepithelial component with immunohistochemical staining of p63. p63 is expressed in the myoepithelial cells and strictly in the nuclei ( $\times 200$  magnification). (C) High-power photomicrograph showing an adenomyoepithelial component with immunohistochemical staining of EMA. EMA is expressed in the membrane of the epithelial cells ( $\times 200$  magnification). (D) Low-power photomicrograph showing myoepithelial carcinoma on H&E staining. The tumor shows multilobulated collections of monomorphic, polygonal, epithelial, or spindled cells, with multiple necrotic foci ( $\times 40$  magnification). (E) Low-power photomicrograph showing myoepithelial carcinoma with immunohistochemical staining of p63. p63 is expressed in the nuclei of the myoepithelial cells ( $\times 40$  magnification). (F) Low-power photomicrograph showing myoepithelial carcinoma with immunohistochemical staining of EMA. The luminal ductal epithelial component stains for EMA ( $\times 40$  magnification). H&E, hematoxylin and eosin; EMA, epithelial membrane antigen.

Up to 40% of the myoepithelial carcinomas reported in the literature metastasized, and most of these metastases were hematogenous.<sup>3</sup> To date, 14 cases of myoepithelial carcinoma of the breast have been reported with distant metastases, including

case 1 of the present study (Table 1).<sup>4-6,8-17</sup> The median age of the metastatic cases was 58 years (range, 42–86 years), and the mean size of the primary tumor was 6.5 cm (range, 2–17 cm). The mitotic counts ranged from 3 to 37 per 10 HPFs.



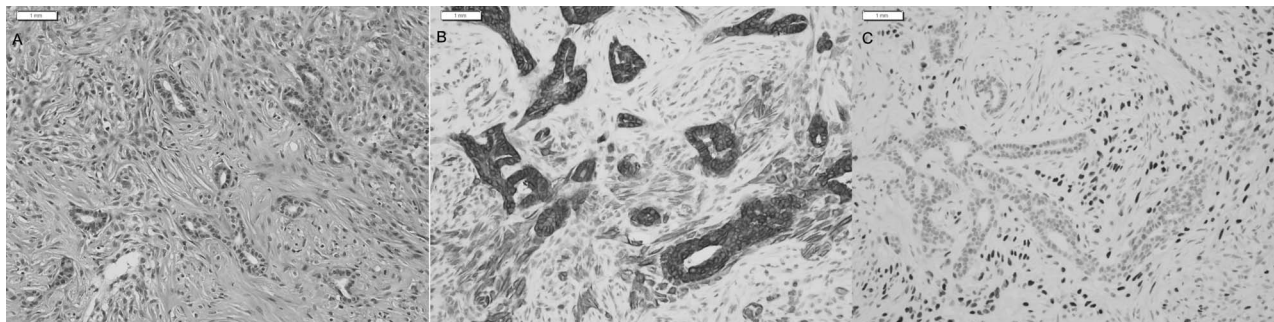
**Fig. 4** Imaging studies and gross photograph of case 2. (A) Mammography of case 2 shows an indistinctly margined, irregularly shaped, hyperdense mass in the right upper outer quadrant (mediolateral oblique view). (B) On magnetic resonance imaging of case 2, a spiculated, irregularly shaped, peripheral enhancing mass is seen in the right upper midportion, about  $2.3 \times 2.1$  cm. (C) Gross appearance of the tumor reveals relatively well-circumscribed, ovoid, grayish mass with multifocal hemorrhagic changes.

Metastases occurred mostly in the lungs, but also occurred in the liver, bone, and brain and at other sites.<sup>5,8,9,17</sup> A total of 1 thyroid,<sup>13</sup> 1 chest wall,<sup>9</sup> and 1 liver metastasis<sup>15</sup> were recorded. Time to progression varied in the 14 cases. In case 1 of the current study, lung metastasis was observed only 6 months after the initial surgery. Michal *et al* reported lung metastasis within 5 months of surgery,<sup>5</sup> and Chen *et al* reported bone metastasis within 3 weeks of surgery.<sup>6</sup> However, for most cases, the time from initial treatment to distant metastasis was  $>21$  months.

By contrast, lymphatic metastasis is rare in malignant AME. There is no indication for an axillary lymph node dissection for these lesions unless clinically detected lymphadenopathy is present, as metastasis to the nodes is unusual.<sup>1</sup> Among the 13 cases, only 2, including case 1 of the current

study, exhibited axillary lymph node metastasis. Chen *et al* previously reported 1 case of myoepithelial carcinoma with axillary lymph node metastasis.<sup>6</sup> In that case, bone metastasis was observed only 3 weeks after initial treatment, and the patient died 7 months after the initial treatment.<sup>6</sup> In case 1 of the present study, there was 1 metastatic axillary lymph node; an axillary lymph node dissection was performed, and the patient had a poor prognosis. The prognostic implication of axillary lymph node metastasis is not well understood, as axillary lymph node metastasis is rare in myoepithelial carcinoma. However, the 2 cases with lymph node metastasis suggest that it may be associated with a poor prognosis.

In case 1 of the present study, following adjuvant chemotherapy, lung metastasis was found on chest CT scan only 6 months later. As the tumor size was



**Fig. 5** H&E stain and immunohistochemical stain of case 2. (A) High-power photomicrograph shows myoepithelial carcinoma in H&E stain. (B) High-power photomicrograph shows myoepithelial carcinoma with immunohistochemical stain of cytokeratin. The luminal cells show positive immunostaining for cytokeratin. (C) High-power photomicrograph shows myoepithelial carcinoma with immunohistochemical stain of p63. The myoepithelial cells exhibit positive nuclear immunostaining for p63 ( $\times 200$ ).



Table 1 Malignant adenomyoepitheliomas of the breast with distant metastases

Reference	Year published	Age (yr)	Tumor size (cm)	Mitoses (n/10HPF)	Initial treatment	Site of distant metastases	Time to distant metastases	Outcome (time)	Axillary lymph node metastasis
Trojani <i>et al</i> <sup>8</sup>	1992	51	2	+	Excisional biopsy	Lung	2 yr	Not described	None
Loose <i>et al</i> <sup>9</sup>	1992	42	3.5	+	Excisional biopsy	Chest wall Lung Brain	29 mo 54 mo 60 mo	Death (64 mo)	None
Michal <i>et al</i> <sup>5</sup>	1994	77	10	+	Excisional biopsy	Lung	5 mo	Death (5 mo)	None
Chen <i>et al</i> <sup>6</sup>	1994	54	17	+	MRM	Bone	3 wk	Death (7 mo)	Present in 1 lymph node
Foschini <i>et al</i> <sup>10</sup>	1995	60	4	Not described	Lumpectomy	Lung	21 mo	Death (3 yr)	None
Rasbridge <i>et al</i> <sup>11</sup>	1998	76	15	+	Wide local excision	Brain	36 mo	Death (36 mo)	None
Simpson <i>et al</i> <sup>4</sup>	1998	50	4	+	Lumpectomy	Lung	25 mo	Death (39 mo)	None
Takahashi <i>et al</i> <sup>12</sup>	1999	60	9	Not described	MRM	Lung, bone	38 mo	Death (43 mo)	None
Bult <i>et al</i> <sup>13</sup>	2000	52	Not described	+	MRM	Thyroid	12 yr	Death (154 mo)	None
Kihara <i>et al</i> <sup>14</sup>	2001	86	4.0	+	Simple mastectomy with sampling of lymph nodes	Lung	3 mo	Death (3 mo)	None
Jones <i>et al</i> <sup>15</sup>	2003	71	3	+	Segmental mastectomy with axillary node dissection	Liver	2 yr	Death (2 yr)	Present in 1 lymph node
Honda <i>et al</i> <sup>16</sup>	2009	53	5	+	MRM	Lung	2 yr	Alive (5 yr)	None
Korolczuk <i>et al</i> <sup>17</sup>	2016	56	3.1	+	MRM	Lung, kidney	5 yr	Alive (31 mo)	None
Present case	—	67	5	+	MRM	Lung Lung Brain	5 yr 6 mo 18 mo	Death (21 mo)	Present in 1 lymph node

>2 cm and the tumor exhibited high-grade malignant transformation,<sup>2</sup> this patient was at high risk of metastasis and a poor prognosis. The role of chemotherapy in the management of AME with carcinoma is not proven. According to previously reported cases with distant metastases, AME with carcinoma responds poorly to chemotherapy and has a poor prognosis. The role of radiotherapy also lacks objective evidence. Generally, in AME, immunohistochemical stains for estrogen and progesterone receptors are negative, as is HER2.<sup>2</sup> Therefore, tamoxifen will not be effective for the treatment of AME or AME with carcinoma. In the present cases, immunohistochemical stains for estrogen, progesterone, and HER2 receptors were all negative; therefore, the patients were not treated with hormone therapy or anti-HER2 therapy.

In conclusion, the present study reported 2 cases of AME with myoepithelial carcinoma, 1 of which exhibited metastatic involvement of an axillary lymph node, as well as lung and brain metastases. It is difficult to diagnose AME with myoepithelial carcinoma due to its unusual morphologic features. Therefore, precise diagnosis is important, with the use of relevant immunohistochemistry. The prognosis of AME with myoepithelial carcinoma is poor and the optimal treatment is not proven; therefore, close follow-up and adequate treatment with surgery and adjuvant chemotherapy or radiotherapy should be considered.

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